CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40249

CORRESPONDENCE

ANDA 40-249

SEP 15 1997

Kiel Laboratories, Inc.
Attention: Jeffrey S. Kiel
2225 Centennial Drive
Gainesville, GA 30504

Dear Sir:

Reference is made to the Abbreviated New Drug Application, submitted on February 17, 1997, for Orphenadrine Citrate Extended-Release Tablets, 100 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Dissolution testing should be conducted on 12 individual test and reference tablets used in the bioequivalence studies. Dissolution profiles should be generated in aqueous media of four different pH ranges as described in "Guidance: Oral Extended (controlled) Release Dosage Forms *In Vivo* Bioequivalence And *In Vitro* Dissolution Testing". Please follow the general dissolution conditions as described in this guidance.

2. In the informed consent form, vol.1.2 pages 132-138, page 1 names orphenadrine citrate tablets and Norflex® tablets as the test and reference drugs; while page 2 states that test drug will be glyburide (Invamed) and the reference drug will be Glynase (Upjohn). Pages 2 to 7 of the consent form do not appear to belong to this study. Approved by the on 9/10/96 is written at the bottom of each page of this informed consent. Please clarify.

3. Chromatograms: We noted that though the sample peaks are larger than the internal standard peaks, they have lower integrated height numbers (e.g. page 300 vol.1.2: the sample peak height is only 29,422 compared with the internal standard peak at 114,767 whereas sample peak appears about 1.5 times bigger than internal standard peak). Please clarify. Was the attenuator setting changed between the two peaks during the run? If yes, how would it affect the baseline and calculation of analyte to internal standard peak ratio? In some runs, it forms new baseline after the elution of internal standard (and change in attenuator setting?); e.g. pages 1118-1123, vol. 1.3. Please describe in detail what exactly was done.

4. Please submit all SOPs for analytical methods.

5. Please explain why plasma orphenadrine concentrations were undetectable in subject #9, period II, food study.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-249

Kiel Laboratories
Attention: Jeffery S. Keil, Ph.D.
2225 Centennial Drive
Gainesville, GA 30504

MAY 1 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 17, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Orphenadrine Citrate Extended-release Tablets, 100 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You have referred to the incorrect dosage form throughout your application. The correct dosage form is extended-release tablets. Please correct your form FDA 356h and other references throughout your application to reflect the correct dosage form, including your 505(j)(2)(A) information. Please refer to Approved Drug Products With Therapeutic Equivalence Evaluations, 16th Edition for information regarding reference listed drugs and dosage forms.
>
> Packaging records and labeling reconciliation records should be included as part of your master production batch record. In addition to packaging reconciliation, you should also include labeling records and labeling reconciliation as part of your executed batch records. Please refer to the Office of Generic Drugs Policy and Procedure Guide # 41-95 regarding Guidance on the Packaging of Test Batches.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Cecelia Parise

Project Manager
(301) 594-0315

Sincerely yours,

/S/

Jerry Phillips 5/1/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

KIEL LABORATORIES, INC.

March 26, 1998

ORIG AMENDMENT

BIOAVAILABILITY
N/A B

Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: **ANDA 40 - 249**
Orphenadrine Citrate Extended - release Tablets, 100 mg

Subject: **Response to Bioequivalence Correspondence Dated September 15, 1997**

Dear Dr. Patnaik:

Reference is made to your letter dated September 15, 1997 concerning the bioequivalence data submitted in Abbreviated New Drug Application (ANDA) 40 - 249 for Orphenadrine Citrate Extended - release Tablets, 100 mg.

Kiel Laboratories, Inc. hereby submits responses to all comments/questions communicated in the referenced letter concerning the comparative dissolution studies and the bioequivalence data submitted in support of the two (2) definitive *in vivo* bioequivalence studies using 100 mg Orphenadrine Citrate Extended - release Tablets.

This amendment is submitted in one (1) volume, an archival copy (blue) and a bioequivalence review copy (orange).

Please direct any written communications regarding this bioequivalence submission to me at the address listed below. If you have any questions or require additional information, please feel free to contact me at (770) 534 - 0079. Facsimile correspondence can be sent to (770) 534 - 0229.

Sincerely,

Jeffrey S. Kiel, Ph.D.
President

RECEIVED
MAR 3 0 1998
GENERIC DRUGS

2225 CENTENNIAL DRIVE • GAINESVILLE, GEORGIA 30504 • 770-534-0079 • FAX 770-534-0229

KIEL LABORATORIES, INC.

April 16, 1998

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Md 20857

ORIG AMENDMENT

RE: MAJOR AMENDMENT TO ANDA 40 - 249
Orphenadrine Citrate Extended - release Tablets, 100 mg

Dear Dr. Patel:

Reference is made to a facsimile dated November 10, 1997 concerning major deficiencies in our Abbreviated New Drug Application 40 - 249 for Orphenadrine Citrate Extended - release Tablets, 100 mg. Kiel Laboratories, Inc. (Kiel) submits today responses to all chemistry deficiencies communicated in the Major amendment notification. In addition, the responses to labeling deficiencies are addressed in the draft labeling that is included in this amendment. A copy of your deficiency letter is also included.

This major amendment is submitted in one (1) volume. Kiel is filing an archival copy (blue folder) and a technical review copy (red) of this submission.

We certify that a true copy of this amendment has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any communications regarding this ANDA to me at the address or telephone number listed below. If you have any questions or require additional information, please feel free to contact Tanyja Scott at (770) 534 - 0079.

Best Regards,

Jeffrey S. Kiel, Ph.D.
President

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KIEL LABORATORIES, INC.

November 25, 1998

FA

FDA ORIG AMENDMENT

Lt. Denise Huie
Project Manager
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20857

VIA FACSIMILE and
UPS Overnight Delivery

RE: **ANDA 40-249**
Orphenadrine Citrate Extended-release Tablets, 100 mg

Subject: **TELEPHONE AMENDMENT**

Dear Lt. Huie:

Reference is made to your telephone conversation on November 24, 1998 regarding ANDA 40 - 249 for Orphenadrine Citrate Extended-release Tablets, 100 mg. The participants of the telephone conversation included yourself, Shirley Brown, OGD chemist and Jeff Kiel, Kiel Laboratories, Inc. This correspondence is in response to the **Telephone Amendment** request.

This telephone amendment is submitted in one (1) volume. For ease of review, your questions/comments have been paraphrased and a detailed response immediately follows each comment.

We certify that a true copy of this amendment has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any communications regarding this ANDA to me at the address or telephone number listed below. If you have any questions or require additional information, please feel free to contact Tanyja Scott at (770) 534 - 0079.

RECEIVED

DEC 0 3 1998

Best Regards,

Jeffrey S. Kiel, Ph.D.
President

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FPL

KIEL LABORATORIES, INC.

November 10, 1998

NEW CORRESP
NC to
FA

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20857

VIA FACSIMILE and UPS
OVERNIGHT DELIVERY

RE: **ANDA 40 - 249: Orphenadrine Citrate Extended-release Tablets, 100 mg**
Subject: **FACSIMILE AMENDMENT**

Dear Dr. Patel:

Reference is made to your facsimile correspondence dated October 22, 1998 concerning deficiencies in our Abbreviated New Drug Application 40 - 249 for Orphenadrine Citrate Extended-release Tablets, 100 mg. Kiel Laboratories, Inc. (Kiel) submits today responses to all chemistry deficiencies communicated in the FACSIMILE amendment notification. In addition, the responses to labeling deficiencies are addressed in the final printed labeling that is included in this amendment. Please note, for your convenience we have included a side-by-side comparison of our final printed labeling with our last submission.

This facsimile amendment is submitted in one (1) volume. Kiel is filing an archival copy (blue folder) and a technical review copy (red) of this submission.

We certify that a true copy of the technical section of this amendment has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any communications regarding this ANDA to me at the address or telephone number listed below. If you have any questions or require additional information, please feel free to contact Tanyja Scott at (770) 534 - 0079.

Best Regards,

Jeffrey S. Kiel, Ph.D.
President

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KIEL LABORATORIES, INC.

VIA [illegible] FA

December 14, 1998

Michael Smela, Jr.
Team Leader
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20857

VIA FACSIMILE and
UPS Overnight Delivery

RE: **ANDA 40 - 249**
Orphenadrine Citrate Extended-release Tablets, 100 mg

Subject: **TELEPHONE AMENDMENT**

Dear Mr. Smela:

Reference is made to your telephone conversation on December 14, 1998 regarding ANDA 40 - 249 for Orphenadrine Citrate Extended-release Tablets, 100 mg. The participants of the telephone conversation included yourself, Shirley Brown, OGD chemist and Tanyja Scott, Kiel Laboratories, Inc. This correspondence is in response to the **Telephone Amendment** request.

This telephone amendment is submitted in one (1) volume. Kiel Laboratories, Inc. certifies that a true copy of this amendment has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any communications regarding this ANDA to me at the address or telephone number listed below. If you have any questions or require additional information, please feel free to contact Tanyja Scott at (770) 534 - 0079.

Best Regards,

Tanyja Y. Scott /for

Jeffrey S. Kiel, Ph.D.
President

RECEIVED
DEC 15 1998
GENERIC DRUGS

KIEL LABORATORIES, INC.

May 7, 1997

ORIG AMENDMENT

N/A

Ms. Cecilia Parise
Project Manager
FOOD AND DRUG ADMINISTRATION
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-249 ORPHENADRINE CITRATE EXTENDED RELEASE TABLETS, 100 MG

Dear Ms. Parise:

Enclosed is Kiel Laboratories' response to your letter of refusal to file dated May 1, 1997. We have revised the product name on each affected page of the original submission. The revised pages are included in the enclosed amendment. To make review easier, we have included in the table of contents the page number from the original submission alongside the page number in this amendment.

A copy of the completed Packaging Work Order for the submission batch was included in pages 2509 - 2511 of the application. A copy of the completed Batch Yield form was on page 2512 of the application. We inadvertently did not include a copy of the Label Reconciliation in the application. This is included in the enclosed amendment (pages 45 - 46). Packaging records and labeling records are attachments to the master batch production record. We have included a copy of the Packaging Work Order, a copy of the Label Reconciliation Form and a copy of the Batch Yield Form as attachments to the proposed Master Batch Record in the amendment (pages 38 - 41).

Also enclosed are three additional copies of the analytical methods for: Assay of the bulk active ingredient and finished dosage form; and Dissolution of the finished dosage form. These are included in 3 folders separate from the amendment.

Please let us know if further information is needed.

Sincerely,

RECEIVED
MAY 12 1997
GENERIC DRUGS

Jeffrey S. Kiel, Ph.D.
President

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KIEL LABORATORIES, INC.

February 17, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville,MD 20855-2773

RE: ANDA for Orphenidrine Citrate Tablets, 100 mg

Dear Mr. Sporn

Kiel Laboratories, Inc. (Kiel) submits today an original abbreviated new drug application (ANDA) seeking approval to market Orphenidrine Citrate Tablets, 100 mg, that are bioeqivalent to the listed drug, Norflex™ (orphenadrine citrate tablets), manufactured by 3M Pharmaceuticals pursuant to NDA # 12157.

The facility for manufacturing of this dosage form is Kiel Laboratories, Inc., located at 2225 Centennial Drive in Gainesville, Georgia.

In accordance with the study protocols, Kiel conducted two definitive *in vivo* bioequivalence studies using 100 mg Orphenidrine Citrate Tablets.
conducted these studies on the behalf of Kiel Laboratories, Inc., and Kiel Laboratories, Inc., has the right to use this clinical study for the ANDA submission.

Orphenidrine Citrate Tablets, 100 mg, are stable and a two year expiration dating is requested for all package sizes. The two year dating is supported by accelerated stability testing.

This ANDA is submitted in three (3) copies. Kiel is filing an archival copy (in blue folders) of the application that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section. A separate copy of the Bioequivalence section is provided (in orange folders) and includes a computer disk, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

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To: Mr. Douglas L. Sporn
Subject: ANDA for Orphenadrine Citrate Tablets, 100 mg

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary - Organization of the ANDA" which follows this letter.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any written communications regarding this ANDA to me at the above address. If you have any quesions or require any additional information, please feel free to contact me at (770)534-0079.

Thank you for your prompt handling of this submission.

Sincerely,

Jeffrey S. Kiel, Ph.D.
President

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